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Detection of a Cryptic Translocation in a Family With Mental Retardation Using FISH and Telomere Region-Specific Probes

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Cryptic rearrangements involving the telomeres are thought to account for a substantial number of patients with unexplained mental retardation and multiple congenital anomalies, although the exact incidence of these rearrangements is still unclear. With the advent of chromosome-specific telomeric probes and the use of FISH (fluorescence in situ hybridization), it is now possible to identify submicroscopic rearrangements of the distal ends of chromosomes that may otherwise go undetected using conventional cytogenetic studies. We report on a 4½ year-old girl with severe mental retardation and minor anomalies who inherited the unbalanced product of a cryptic translocation involving chromosomes 2 and 17 from her father. The family history was significant for early pregnancy losses, stillbirths, and mental retardation in many other family members, suggesting segregation of a familial translocation. This translocation was detected using chromosome-specific telomere FISH probes, and not visible using conventional cytogenetic methods. Collectively, this case and those previously reported clearly demonstrate the value of a systematic search for cryptic chromosome rearrangements in patients with unexplained mental retardation with previously reported normal chromosome studies; and in particular those with a family history of mental retardation, birth defects, or early pregnancy losses. Am. J. Med. Genet. 92:250–255, 2000. © 2000 Wiley-Liss, Inc.

KEY WORDS: cryptic translocation; chromosome-specific telomere probes; fluorescence in situ hybridization (FISH); partial trisomy 17; partial monosomy 2; multiple congenital anomalies

INTRODUCTION

With the advent of new molecular techniques and fluorescence in situ hybridization (FISH), it is now possible to detect chromosome abnormalities that would otherwise go unnoticed by conventional cytogenetic banding techniques. The incidence of these cryptic rearrangements is still unclear, although some studies suggest ranges from 6 to 7.4% of cases of idiopathic mental retardation [Flint et al., 1995; Giraudeau et al., 1997]. The testing of cryptic translocations by the use of chromosome-specific telomeric probes was first proposed by Ledbetter, who described a hypothetical set of probes designed for this application [Ledbetter, 1992]. He proposed the use of telomere, region-specific probes to be used in FISH to search for cryptic rearrangements. Since then, unique sequences proximal to the $(TTAGGG)_n$ tandem repeats present at the telomeres [Brown et al., 1990; Cross et al., 1990; Moyzis et al., 1988; Wilkie et al., 1991] have been developed as telomere-specific probes [National Institutes of Health and Institute of Molecular Medicine Collaboration, 1996; Knight et al., 1997].

The first case of a cryptic translocation was described in a boy who presented with α-thalassemia, minor anomalies, and mental retardation who had an apparently normal karyotype [Wilkie et al., 1990]. Further molecular studies showed a deleted 16p that resulted from the unbalanced product of a 1;16 maternal cryptic translocation. He had a sister with mental retardation and no hematological problems who inherited the maternal derivative chromosome 1. Other reports of cryptic translocations quickly followed, involving clinically well-known disorders that prompted the systematic search for cryptic anomalies. These cases included patients with cri-du-chat [Overhauser et al., 1989], Wolf-

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Hirschhorn syndrome [Altherr et al., 1991], and Miller-Dieker syndrome [Kuwano et al., 1991]. The Miller-Dieker reports involved a patient with a half-cryptic translocation with a known 17p derivative chromosome, later found to be part of a translocation with distal 3q. Another was a case of a full-cryptic translocation involving 17p. It was not until recently that complete sets of chromosome-specific telomeric probes became available to look for cryptic rearrangements in the clinical setting [National Institutes of Health and Institute of Molecular Medicine Collaboration, 1996; Knight et al., 1997].

We report on a family with a cryptic translocation between chromosomes 2 and 17, detected using chromosome-specific telomeric FISH probes. This family was previously studied using conventional G-banding in three different laboratories, and no visible rearrangements were detected. Using chromosome-specific telomeric FISH probes, the proband was found to have inherited an unbalanced segregant from her father, which resulted in partial trisomy for distal 17q and partial monosomy for distal 2q.

MATERIAL AND METHODS

Clinical Studies

A 4½-year-old girl presented to the Genetics Clinic at Texas Children's Hospital with severe mental retardation and minor anomalies. She was born at 36 weeks of gestation via cesarean section, due to breech presentation, to a 27-year-old G1 woman. The family is of Iranian/Russian descent and consanguinity was denied. Her birth weight was 2700 g. The neonatal period was complicated by respiratory distress and jaundice. She was discharged at age 1 week. At birth, the girl was noted to have minor anomalies prompting a genetic evaluation. She also had significant hypotonia and was diagnosed with congenital dislocation of the right hip, which required surgical reduction, casting, and placement of a harness. The treatment failed to reduce the dislocation, and a second hip surgery was performed at age 4 years. Seizures were diagnosed at age 3½ years and were characterized by staring episodes and an abnormal EEG. She was treated with Depakote and the seizures decreased in number. The developmental history showed global developmental delay noted early in infancy. At the time of the clinical evaluation at age 4½ years, she was unable to sit unsupported. She started rolling over at approximately 2 years 9 months of age. She held her head up at age of 3½ years. She had no speech, and did not understand simple commands. Results of an extensive work-up, including biochemical studies, a muscle biopsy, and chromosome studies, were normal.

Multiple children on the paternal side of the family had severe developmental delay, minor anomalies, and early death (Fig. 1). The proposita's half sister through her father is 13 years old and by report, shares many findings with our patient. She has a partial duplication of the right kidney, pulmonary artery branch stenosis, minor anomalies, and mental retardation. Several sibs of the father had children with multiple congenital anomalies, mental retardation, and early infant death. In the father's sibship there was also a report of six spontaneous miscarriages during the first trimester (II-14 to II-19). One paternal uncle (II-4) had four normal children and one daughter who died at age 14 months with minor anomalies, reportedly similar to the ones seen in the proposita. A second paternal uncle (II-6) had five normal children, two pregnancies that ended in first trimester miscarriages (III-10 and III-11), and three other children deceased early in life of unclear medical problems. Two of those were girls, both deceased, one at age 9 months (III-8) and the other one at age 13 months (III-15) with multiple congenital anomalies. Another male (III-12) died at age 9 years and carried the diagnosis of "Down syndrome." More specific details about his clinical history were not available. A paternal uncle in the family (II-10) had a daughter (III-19) who died at 2 days of age of congenital heart disease. Individual II-12 in the pedigree died very early in infancy; no clinical information is currently available. A paternal aunt (II-13) is reportedly sterile.

Physical Findings

The patient (Fig. 2) was small for age with a weight of 10 kg (<3rd centile, 50th centile for 14 months), length of 90 cm (<3rd centile, 50th centile for 28 months), and OFC of 48 cm (<3rd centile, 50th centile for a 23-month-old). She had microcephaly; tall forehead; curly hair with a widow's peak; downslanting palpebral fissures; hypertelorism; midface hypoplasia; mild synophrys; arched eyebrows; and very long eyelashes. Her nose was small and short with anteverted

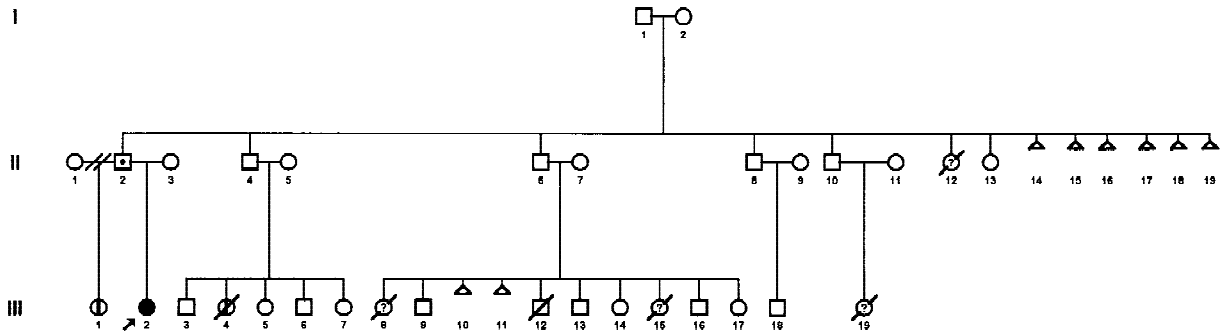

Fig. 1. Pedigree: ■ ● affected; □ ○ unaffected; ◫ ◑ affected (hearsay); ⊡ ⊙ carrier; △ spontaneous abortion; ? possibly affected.

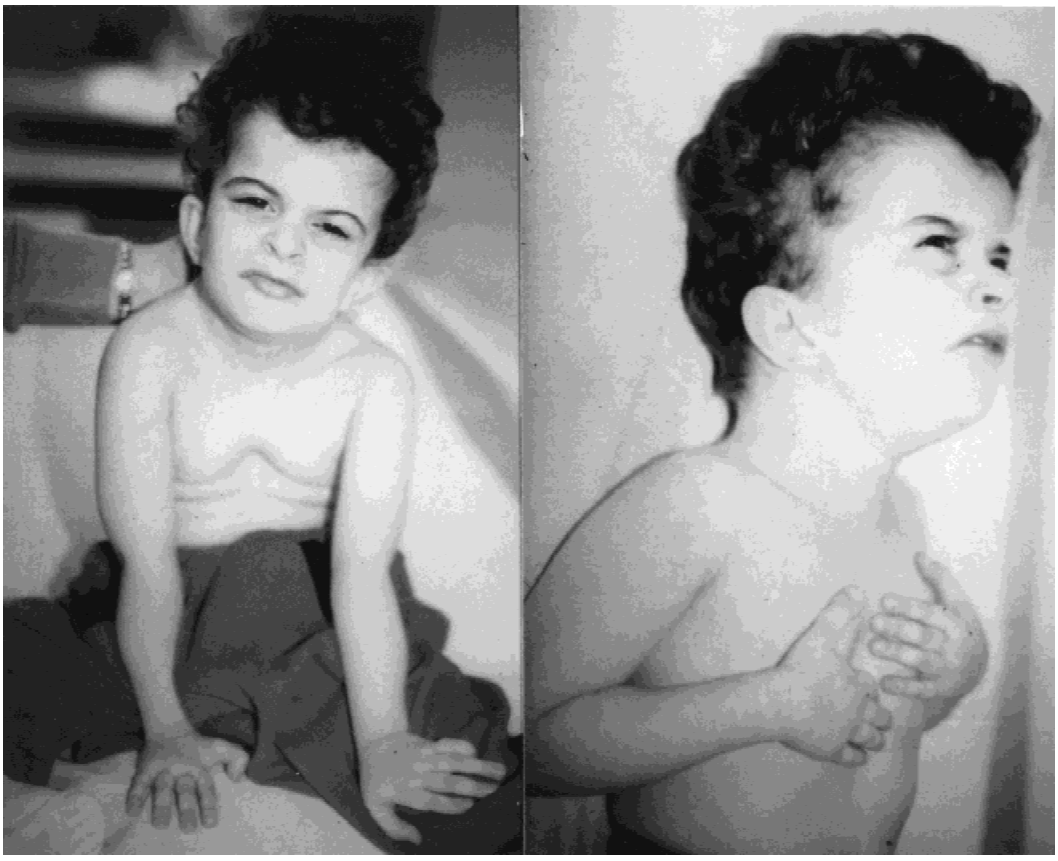

Fig. 2. Profile and anterior view of the proposita at age 4½ years. Note unusual facial appearance, redundant hand skin folds, and joint hypermobility.

nares and hypoplasia of the alae nasi. Her ears were large with simple helices, slightly posteriorly rotated, and apparently low set. Uvula was bifid, and she had a high-arched palate, redundant skin in the posterior aspect of the neck and upper back, a pectus carinatum with prominence of the midsternum and asymmetry of the chest due to left-sided prominence of the costal cage. Redundant skin folds over the hands and feet gave a wrinkled appearance. Her thumbs were proximally placed and broad, and her fingers were long with square fingertips. Prominent fetal pads were noted on all fingers. Her toes were broad with sandal-gap deformities seen bilaterally. She had severe hypotonia with poor head and trunk control. During the exam, she had waving and flapping motions of the hands.

Cytogenetic Studies

Chromosome analyses performed by routine GTG-banding on peripheral blood on the proposita and her father showed apparently normal karyotypes. Simultaneous FISH for all telomeric regions was performed according to the manufacturer's specifications (Cytocell, Ltd., Oxford, UK) and as previously published [Knight et al., 1997]. Chromosomes of the proposita and her father were hybridized in 23 different squares on a microscope slide (one for each autosome and one for the sex chromosomes) to detect chromosome-specific telomeric-region rearrangements. The hybridization pattern was normal in all squares except for chromosomes 2 and 17. The probes used in the telomere device for chromosomes 2 and 17 were PAC dJ1011017 for 2q and PAC 362K4 for 17q. The proposita's father's analyses showed a lack of hybridization signal for the 2q probe on one chromosome 2 and hybridization to the end of the distal long arm of one E group chromosome (Fig. 3A). Additionally, the square for chromosome 17 showed lack of hybridization to the distal long arm of one chromosome 17, with hybridization to the distal end of an A group chromosome (Fig. 3B). Subsequently, FISH analyses on the proposita showed lack of hybridization on the distal long arm of one chromosome 2 (Fig. 3C). For chromosome 17, there were three areas of hybridization, two on both chromosomes 17q plus an additional signal corresponding to 17q material hybridizing to the distal long arm of an A group chromosome, presumably chromosome 2 (Fig. 3D). Therefore, the proposita inherited the unbalanced product of a paternal 2;17 translocation that resulted in monosomy for distal 2q and trisomy for distal 17q. On closer examination of the GTG-banded karyotype, no rearrangements of chromosomes 2 and/or 17 were observed in either the proposita or her father. A composite of chromosomes 2 and 17 in the child (Fig. 4A) and the father (Fig. 4B) are shown.

DISCUSSION

We report on a family with a cryptic translocation involving chromosomes 2 and 17 detected by FISH us-

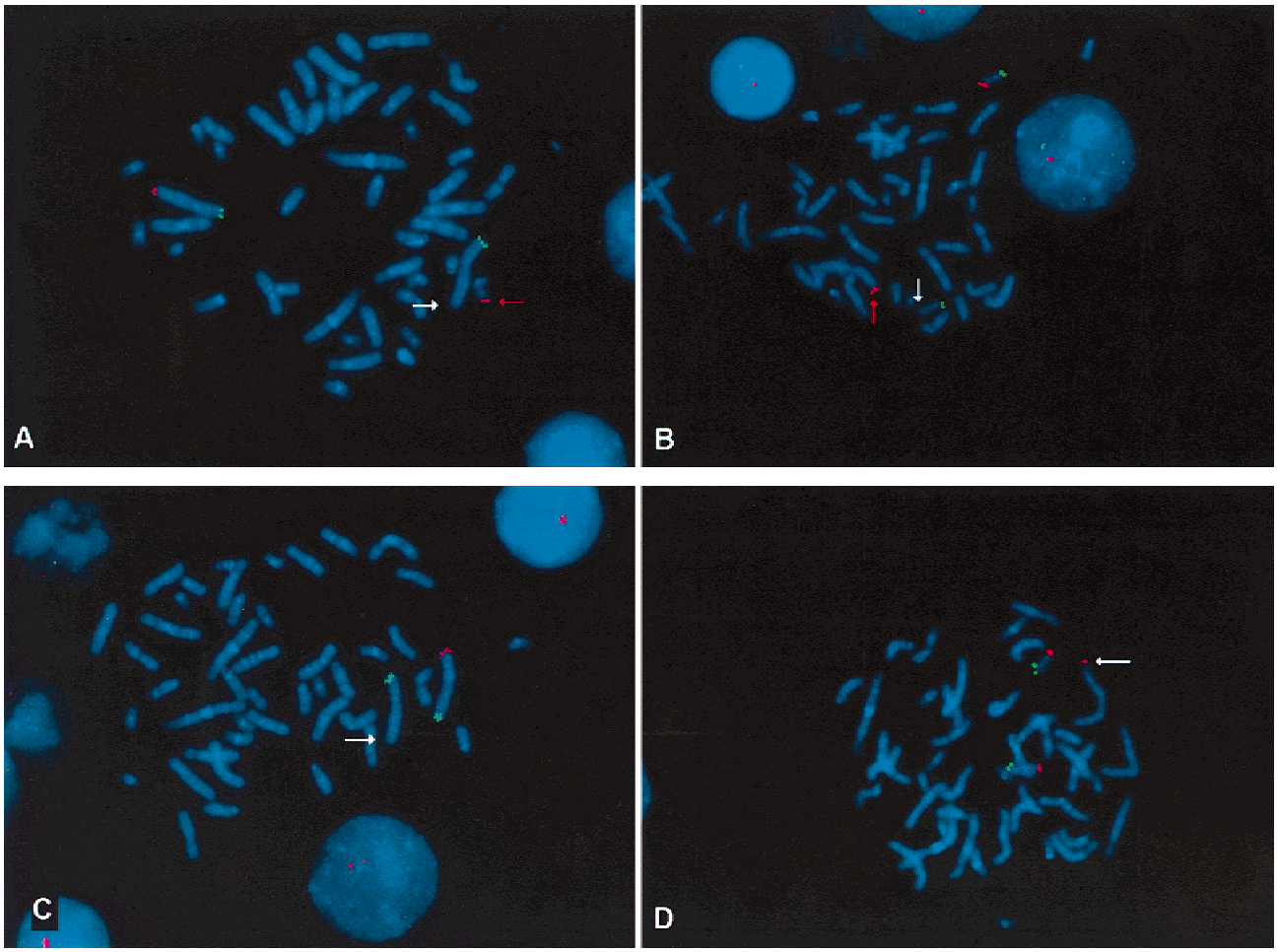

Fig. 3. FISH studies on metaphase spreads with telomere region-specific probes for chromosomes 2 and 17. The probes for the long arms fluoresce red while the short arm signals fluoresce green. **(A)** Hybridization with chromosome 2 telomere region-specific probes on the proposita's father. A white arrow indicates a missing distal signal on chromosome 2q that is now located on distal 17q (red arrow). **(B)** Hybridization with chromosome 17 telomere region-specific probes on the proposita's father. A white arrow indicates lack of hybridization to the distal long arm of one chromosome 17. A signal for 17q is now seen on distal 2q (red arrow). **(C)** Hybridization with chromosome 2 telomere region-specific probes on the proposita. The arrow indicates the lack of hybridization on one distal 2q. **(D)** Hybridization with chromosome 17 telomere region-specific probes on the proposita. Three hybridization signals for 17q are present in the proposita, two on 17q plus an additional signal hybridizing to the distal long arm of 2q, indicated by the arrow.

ing chromosome-specific telomeric probes. Cytogenetic analysis on the proposita failed to show any abnormalities using conventional G-banded analysis. The presence of multiple congenital abnormalities and the family history of children with multiple anomalies, mental retardation, and early pregnancy losses was highly suggestive of an undetected chromosomal rearrangement.

Full trisomy 17 is lethal, although several reports of mosaic trisomy 17 and partial trisomy 17 have been published [Barros Nunez et al., 1993; Berberich et al., 1978; Bridge et al., 1985; Caine et al., 1989; Cotter and Stewart, 1990; Fryns et al., 1979; Gallien et al., 1981; King et al., 1991; Lenzini et al., 1988; Ohdo et al., 1989; Orye and van Bever, 1985; Robb et al., 1987; Sarri et al., 1997; Shaffer et al., 1996; Shawe et al., 1983; Shimizu et al., 1988; Turleau et al., 1979; Yamamoto et al., 1979].

Most reports involve trisomy for large portions of the long arm of chromosome 17. Only a few reports describe patients with distal trisomy 17q [Caine et al., 1989; Orye and van Bever, 1985; Shimizu et al., 1988].

Patients with trisomy 17q have growth retardation (sometimes associated with growth hormone deficiency), microcephaly, multiple congenital anomalies, and minor anomalies that include high forehead; frontal bossing; high hairline with a widow's peak; narrow palpebral fissures; short nose; large mouth with downturned corners; thin upper lip; and low-set round ears with loped helices. In addition, patients with distal 17q trisomy present with short neck; excess skin; brachyrhizomelia; ligament hyperlaxity; hypoplastic genitalia or cryptorchidism; cerebral anomalies; urinary tract malformations; and cardiac malformations including atrial septum defects and subaortic stenosis. All cases of reported trisomy 17q are associated with severe mental retardation. Many of the findings described in children with trisomy for different regions of 17q share similar signs with our patient suggesting that there may be a critical region on distal 17q responsible for

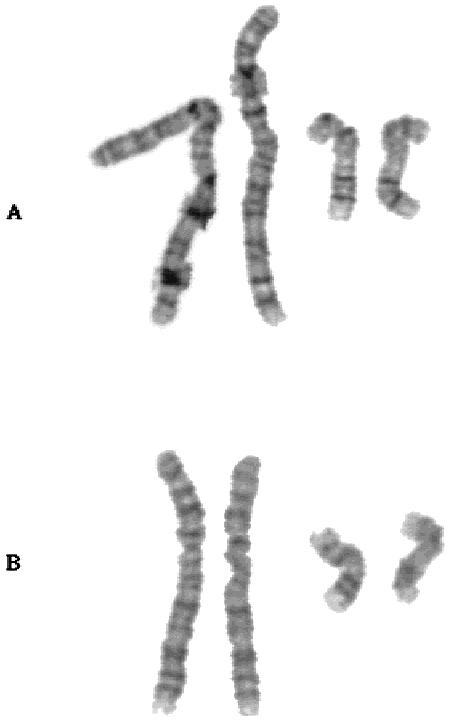

Fig. 4. **(A)** GTG banding of chromosomes 2 and 17 in the proposita. **(B)** GTG banding of chromosomes 2 and 17 in the proposita's father.

most of the phenotype, as suggested by others, emphasizing that most of the features mentioned may be the result of trisomy for 17q23 to qter [Sarri et al., 1997].

On the other hand, the phenotype for distal 2q deletions appears to have significant variability, as shown by multiple reports [Coldwell et al., 1992; Fisher et al., 1994; Gorski et al., 1989; Haag et al., 1993; Lamb et al., 1990; Lin et al., 1992; Oley et al., 1993; Phelan et al., 1993, 1995; Stratton et al., 1994; Wang et al., 1994; Waters et al., 1993]. Some of the reported patients had severe phenotypes with multiple congenital anomalies [Coldwell et al., 1992; Waters et al., 1993] as opposed to others with milder mental retardation and minor facial anomalies [Fisher et al., 1994; Gorski et al., 1989; Lin et al., 1992]. Other patients had, in addition, congenital heart defects such as double outlet right ventricle, ventricular septal defects, and coarctation of the aorta [Fisher et al., 1994; Wang et al., 1994]. Overall, the clinical phenotype is not necessarily related to the size of the deletion, as some of the patients with significant heart disease had very small terminal deletions. Recent reports have shown a group of unrelated patients with distal deletions of 2q whose phenotype is consistent with Albright hereditary osteodystrophy, emphasizing even further the variability of the clinical phenotype in this deletion [Phelan et al., 1993, 1995]. These patients presented with the classic short stature, brachydactyly, round face, and mental retardation. The contribution of the deletion 2q in our patient's phenotype is therefore not clear.

The advent of FISH, and in particular the availability of chromosome-specific telomeric probes, makes this molecular technique a very powerful one to use in the clinical setting. For many years, clinical cytogeneticists have recognized the limitations in detecting small rearrangements in the distal telomeric regions of the chromosomes. Telomeric regions are typically G-band negative and very gene rich. Thus, rearrangements and deletions involving these areas are often associated with significant phenotypic abnormalities including mental retardation and other birth defects. The telomeres consist mostly of a simple tandem repeat of $(TTAGGG)_n$ distal to subtelomeric repeats, some shared by multiple chromosomes, adjacent to proximal unique sequences. These unique sequences begin about 100 to 300 kilobases from the distal end of most chromosomes [Brown et al., 1990; Cross et al., 1990]. In contrast to high-resolution banding techniques in which deletions of no less than 2–3 megabases can be resolved, this type of FISH testing provides a 10-fold increased sensitivity for detecting small rearrangements [National Institutes of Health and Institute of Molecular Medicine Collaboration, 1996].

Cryptic translocations were previously detected with a variety of molecular techniques to assess the integrity of the telomeric regions [Altherr et al., 1991; Blennow et al., 1996; Delneste et al., 1998; Ghaffari et al., 1998; Giraudeau et al., 1997; Horsley et al., 1998; Kuwano et al., 1991; Ning et al., 1996; Overhauser et al., 1989; Precht et al., 1998; Riegel et al., 1999; Wilkie, 1993; Wilkie et al., 1990]. The number of reports is rapidly increasing, presumably due to the availability of these FISH probes for clinical use. Some additional reports also involve prenatal cases [Brackley et al., 1999; Guichet et al., 1998; Senger et al., 1997].

FISH studies for specific telomeric regions may become a standard test to be used in children with unexplained mental retardation with apparently normal chromosomes. This type of testing should also be considered in cases of families with recurrence of multiple congenital anomalies. It can be debated whether this technology should also be used in couples who are being evaluated secondary to multiple miscarriages, in addition to the conventional cytogenetic techniques. The proportion of cryptic translocations in each of these categories is yet to be determined, but is presumed to be a significant, clinically relevant number.

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